

- Cardiology (290)
- Clinical haematology/oncology (171)
- Clinical pharmacology and toxicology (273)
- Clinical sciences (410)
- Dermatology (131)
- Endocrinology (174)
- Gastroenterology (183)
- Infectious diseases and STIs (212)
- Nephrology (104)
- Neurology (247)
- Ophthalmology (56)
- Psychiatry (59)
- Respiratory medicine (162)
- Rheumatology (134)

2600 MCQ with Illustrated Answer
Full Topics Note
14 Chapter

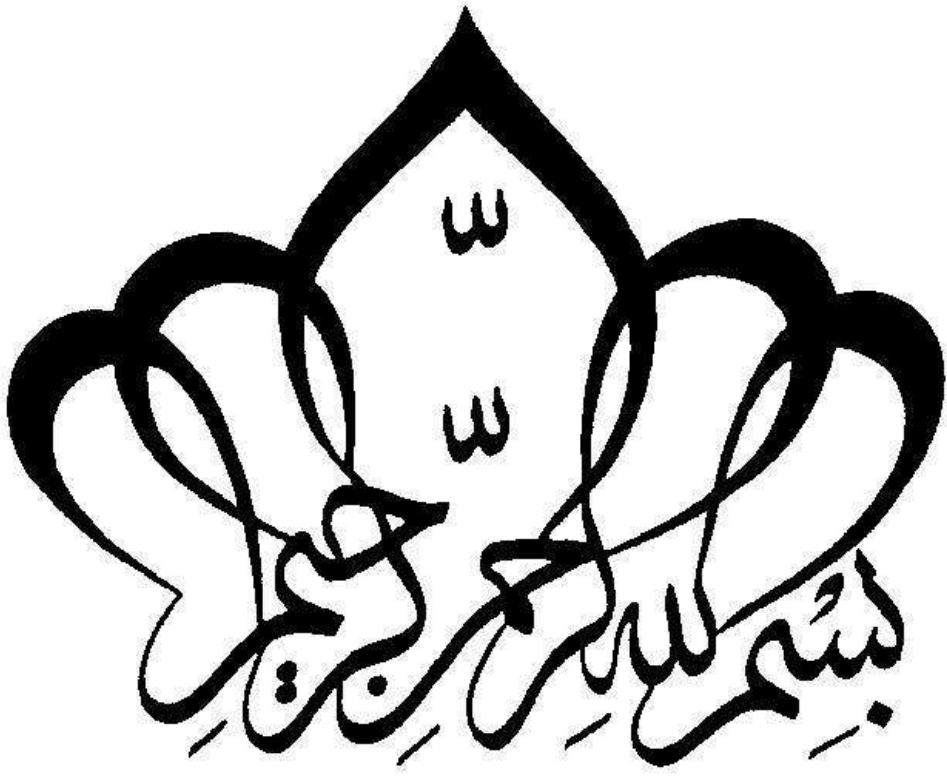
Clinical haematology oncology

P. M MCQ Bank **2017**



VISIT...

LANZAROTE
Caliente.COM



قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا
۞ إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

إهداء

للكل آية من كتاب الله حفظناها ولكل معلومة قرأناها ونسيناها لعل الله يحمينا من النسيان ويروها إلينا
للكل شخص وعونا له في ظهري الغيب لعل الله أن يستجيب وعائنا
للكل مريض قرأله ما أله لعل الله يشفيه ويعير إليه صحته وعافيته
للكل لحظة تألم بها أحببنا لعل الله لا يريهم الألم ولا يضييهم مرة أخرى
للكل موقف اجتجت به عينا فلم تلباني لعل الله لا يضرنني بهما في حياتي
للكل حاتم صاحب أهراف ومباوى لعل الله يحقق له مقاصده حتى يرضيه ويرضى عنه
للكل مجتهد لعل الله يجعل له من التوفيق أوفر حظ ونصيب ويهون له الأسباب كلها من حيث لا يدري من غير ضراء مضرة ولا فتنة مضلة
للكل من فقر شيئا في الحياة لعل الله يعيره إليه أو يعوضه بما يسعده
للكل شخص ابتعدنا عنه لعل الله يجمعه بمن هم أفضل منا
وأخيرا وليس آخرا لأهلنا لعل الله يجعلها لهم صرقة جارية ترو إليهم قليلا من فضلهم علينا وتكون سببا يلم شملنا تحت سقف واحد بعد أن
هجرتنا الحروب والمصائب

يقول أحد الصالحين

إِذَا رَأَيْتَ أَنَّ اللَّهَ وَفَقَكَ لِإِخْوَةِ تَعْيْنِكَ عَلَى الْخَيْرِ.. فَأَعْلَمْ أَنَّ اللَّهَ يَرِيدُ بِكَ خَيْرًا !! وَإِذَا وَفَقَكَ لِلدُّعَاءِ.. فَأَعْلَمْ أَنَّ اللَّهَ يَرِيدُ أَنْ يُعْطِيَكَ !! وَإِذَا
وَفَقَكَ لِقَضَاءِ حَوَائِجِ النَّاسِ فَأَعْلَمْ أَنَّ لَكَ يَتَخَلَّى عَنْكَ !! وَإِذَا وَفَقَكَ لِلزُّكْرِ.. فَأَعْلَمْ أَنَّكَ يُحِبُّكَ !!.. وَإِذَا أُحِبَّكَ أُعْزَكَ.. وَنَصْرَكَ.. وَأُيْرَكَ..
وَأُسْتَجَابَ لِدُعَائِكَ !!

This issue of **MRCPPART1 MADE EASY 2017** contains the following:

- Full topic note.
- Around 2600 MCQs from **PM 2017 BANK** covering 14 chapter in internal medicine
- External links for the related guidelines (such as NICE, SIGN, RCP ...etc).
- Comments with illustrative pictures and links to external media.
- Most Recommended QBank for MRCP Part 1, Arab Board, Jordanian Board and other internal medicine assessment exams.

Please Note that

Each chapter begins with notes section. These notes are repeated under the Questions in the website. In these collections the notes are not repeated under each question except in some to avoid unnecessary repetition. For clarity and convenience the title of the related note is only mentioned after the comments in case the reader want to refer back to the respective note in the notes section.

The illustration below is to show and Example

☐	Minimal change disease
☐	Post-streptococcal glomerulonephritis
☐	Goodpasture's syndrome

Goodpasture's syndrome

- IgG deposits on renal biopsy
- anti-GBM antibodies

• These changes are characteristic of Goodpasture's syndrome.

[Discuss and give feedback](#)

Goodpasture's syndrome

Comment of the Q

title of the note in case the reader want to refer back to the notes sections

MRCPPART1 MADE EASY 2017

Chapter	Number of Q
Cardiology	292
Clinical haematology/oncology	171
Endocrinology	174
Gastroenterology	183
Infectious diseases and STIs	212
Nephrology	104
Neurology	247
Respiratory medicine	162
Rheumatology	134
Clinical pharmacology and toxicology	273
Clinical sciences	410
Dermatology	131
Ophthalmology	56
Psychiatry	59

إعداد وتنسيق

M. HABAYEB

**Msc Internal. Medicine
Cairo University**

&

A. MURAD

لا تنسونا من صالح دعائكم

ما كان من خطأ فمن أنفسنا وما كان من توفيق فمن الله

تم بحمد الله وتوفيقه ومنه

جعل الله عملنا متقبلاً خالصاً لوجهه الكريم

Reference ranges

Reference ranges vary according to individual labs. All values are for adults unless otherwise stated

Full blood count

Haemoglobin	Men: 13.5-18 g/dl Women: 11.5-16 g/dl
Mean cell volume	82-100 fl
Platelets	150-400 * 10 ⁹ /l
White blood cells	4-11 * 10 ⁹ /l

Urea and electrolytes

Sodium	135-145 mmol/l
Potassium	3.5 - 5.0 mmol/l
Urea	2.0-7 mmol/l
Creatinine	55-120 umol/l
Bicarbonate	22-28 mmol/l
Chloride	95-105 mmol/l

Liver function tests

Bilirubin	3-17 umol/l
Alanine transferase (ALT)	3-40 iu/l
Aspartate transaminase (AST)	3-30 iu/l
Alkaline phosphatase (ALP)	30-100 umol/l
Gamma glutamyl transferase (yGT)	8-60 u/l
Albumin	35-50 g/l
Total protein	60-80 g/l

Other haematology

Erythrocyte sedimentation rate (ESR)	Men: < (age / 2) mm/hr Women: < ((age + 10) / 2) mm/hr
Prothrombin time (PT)	10-14 secs
Activated partial thromboplastin time (APTT)	25-35 secs
Ferritin	20-230 ng/ml
Vitamin B12	200-900 ng/l
Folate	3.0 nmol/l
Reticulocytes	0.5-1.5%
D-Dimer	< 400 ng/ml

Other biochemistry

Calcium	2.1-2.6 mmol/l
Phosphate	0.8-1.4 mmol/l
CRP	< 10 mg/l
Thyroid stimulating hormone (TSH)	0.5-5.5 mu/l
Free thyroxine (T4)	9-18 pmol/l
Total thyroxine (T4)	70-140 nmol/l
Amylase	70-300 u/l

Uric acid	0.18-0.48 mmol/l
-----------	------------------

Arterial blood gases

pH	7.35 - 7.45
pCO2	4.5 - 6.0 kPa
pO2	10 - 14 kPa

Lipids

Desirable lipid values depend on other risk factors for cardiovascular disease, below is just a guide:

Total cholesterol	< 5 mmol/l
Triglycerides	< 2 mmol/l
HDL cholesterol	> 1 mmol/l
LDL cholesterol	< 3 mmol/l

Acute lymphoblastic leukaemia: prognostic features	Notes
Acute myeloid leukaemia	Notes
Acute promyelocytic leukaemia	Notes
Alpha-thalassaemia	Notes
Antiphospholipid syndrome	Notes
Antiphospholipid syndrome: pregnancy	Notes
Antithrombin III deficiency	Notes
Aplastic anaemia: management	Notes
Autoimmune haemolytic anaemia	Notes
Beta-thalassaemia trait	Notes
Bladder cancer: risk factors	Notes
Blood films: pathological cell forms	Notes
Blood films: typical pictures	Notes
Blood product transfusion complications	Notes
Burkitt's lymphoma	Notes
Cancer in the UK	Notes
Chemotherapy side-effects: nausea and vomiting	Notes
Chronic lymphocytic leukaemia	Notes
Chronic lymphocytic leukaemia: management	Notes
Chronic lymphocytic leukaemia: prognostic factors	Notes
Chronic myeloid leukaemia	Notes
Coagulopathy of liver disease	Notes
Colorectal cancer	Notes
Colorectal cancer: screening	Notes
Cyclophosphamide	Notes
Cytotoxic agents	Notes
Deep vein thrombosis: diagnosis and management	Notes
Drug-induced haemolytic anaemia	Notes
Drug-induced pancytopenia	Notes
ECOG score	Notes
Eosinophilia	Notes
Factor V Leiden	Notes
G6PD deficiency	Notes
Gastric cancer	Notes
Gastrointestinal secretions	Notes
Gingival hyperplasia	Notes
Haematological malignancies: genetics	Notes
Haematological malignancies: infections	Notes
Haemolytic anemias: by site	Notes
Haemophilia	Notes
Hairy cell leukaemia	Notes
Hepatocellular carcinoma	Notes
Hereditary spherocytosis	Notes
Hodgkin's lymphoma: staging	Notes
Hyposplenism	Notes
IgG4-related disease	Notes
Iron deficiency anaemia	Notes
ITP	Notes
ITP: investigation and management	Notes

Leucocyte alkaline phosphatase	Notes
Leukaemoid reaction	Notes
Macrocytic anaemia	Notes
MGUS	Notes
Myelofibrosis	Notes
Myeloma: features	Notes
Myeloma: prognosis	Notes
Neutropenic sepsis	Notes
Oesophageal cancer	Notes
Paraproteinaemia	Notes
Paroxysmal nocturnal haemoglobinuria	Notes
Polycythaemia	Notes
Polycythaemia rubra vera: features	Notes
Polycythaemia rubra vera: management	Notes
Pregnancy: DVT/PE	Notes
Primary immunodeficiency	Notes
Prostate cancer: PSA testing	Notes
Protein C deficiency	Notes
Pseudohyperkalaemia	Notes
Sickle-cell crises	Notes
Sideroblastic anaemia	Notes
Sjogren's syndrome	Notes
Superior vena cava obstruction	Notes
Thrombocytosis	Notes
Thrombophilia: causes	Notes
Thrombotic thrombocytopenic purpura: management	Notes
Thymoma	Notes
Tumour lysis syndrome	Notes
Tumour markers	Notes
Venous thromboembolism: risk factors	Notes
Vitamin B12 deficiency	Notes
Von Willebrand's disease	Notes
Waldenstrom's macroglobulinaemia	Notes

Acute lymphoblastic leukaemia: prognostic features

Good prognostic factors

- French-American-British (FAB) L1 type
- common ALL
- pre-B phenotype
- low initial WBC
- del(9p)

Poor prognostic factors

- FAB L3 type
 - T or B cell surface markers
 - Philadelphia translocation, t(9;22)
 - age < 2 years or > 10 years
 - male sex
 - CNS involvement
 - high initial WBC (e.g. > 100 * 10⁹/l)
 - non-Caucasian
-

Acute myeloid leukemia

Acute myeloid leukaemia is the more common form of acute leukaemia in adults. It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder.

Poor prognostic features

- > 60 years
- > 20% blasts after first course of chemo
- cytogenetics: deletions of chromosome 5 or 7

Acute promyelocytic leukaemia M3

- associated with t(15;17)
- fusion of PML and RAR-alpha genes
- presents younger than other types of AML (average = 25 years old)
- Auer rods (seen with myeloperoxidase stain)
- DIC or thrombocytopenia often at presentation
- good prognosis

Classification - French-American-British (FAB)

- M0 - undifferentiated
- M1 - without maturation
- M2 - with granulocytic maturation
- M3 - acute promyelocytic
- M4 - granulocytic and monocytic maturation
- M5 - monocytic
- M6 - erythroleukaemia
- M7 - megakaryoblastic

Acute promyelocytic leukaemia

You are not normally expected to be able to differentiate the different subtypes of acute myeloid leukaemia (AML) for the MRCP. An exception to this is acute promyelocytic leukaemia (APML, the M3 subtype of AML). The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management

APML is associated with the t(15;17) translocation which causes fusion of the PML and RAR-alpha genes.

Features

- presents younger than other types of AML (average = 25 years old)
- DIC or thrombocytopenia often at presentation
- good prognosis

Alpha-thalassemia

Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin

Overview

- 2 separate alpha-globulin genes are located on each chromosome 16
- ◆Clinical severity depends on the number of alpha chains present
- ◆If 1 or 2 alpha chains are absent then the blood picture would be hypochromic and microcytic, but the Hb level would be typically normal
- ◆Loss of 3 alpha chains results in a hypochromic microcytic anaemia with splenomegaly. This is known as Hb H disease
- ◆If all 4 alpha chains absent (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops)

Antiphospholipid syndrome

Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

A key point for the exam is to appreciate that antiphospholipid syndrome causes a paradoxical rise in the APTT. This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade

Features

- venous/arterial thrombosis
- recurrent fetal loss
- livedo reticularis
- thrombocytopenia
- prolonged APTT
- other features: pre-eclampsia, pulmonary hypertension

Associations other than SLE

- other autoimmune disorders
- lymphoproliferative disorders
- phenothiazines (rare)

Management - based on BCSH guidelines

- initial venous thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months
- recurrent venous thromboembolic events: lifelong warfarin; if occurred whilst taking warfarin then increase target INR to 3-4
- arterial thrombosis should be treated with lifelong warfarin with target INR 2-3

External Links

DermIS.net

Pictures of livedo reticularis

British Society of Haematology

Antiphospholipid syndrome guidelines

Antiphospholipid syndrome: pregnancy

Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

In pregnancy the following complications may occur:

- recurrent miscarriage
- IUGR
- pre-eclampsia
- placental abruption
- pre-term delivery
- venous thromboembolism

Management:

- low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing
- low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation
- these interventions increase the live birth rate seven-fold

External Links

[RCOG](#)

Recurrent miscarriage guidelines

Antithrombin III deficiency

- ◆ Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:3,000 of the population. Inheritance is autosomal dominant
- ◆ Antithrombin III inhibits several clotting factors, primarily thrombin, factor X and factor IX. It mediates the effects of heparin
- ◆ Antithrombin III deficiency comprises a heterogeneous group of disorders, with some patients having a deficiency of normal antithrombin III whilst others produce abnormal antithrombin III

Features

- recurrent venous thromboses
- arterial thromboses do occur but are uncommon

Management

- thromboembolic events are treated with lifelong warfarinisation
- heparinisation during pregnancy*
- antithrombin III concentrates (often used during surgery or childbirth)

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

Condition	Prevalence	Relative risk of VTE
Factor V Leiden (heterozygous)	5%	4
Prothrombin gene mutation (heterozygous)	1.5%	3
Protein C deficiency	0.3%	10
Protein S deficiency	0.1%	5-10
Antithrombin III deficiency	0.03	10-20

*as patients with antithrombin III deficiency have a degree of resistance to heparin anti-Xa levels should be monitored carefully to ensure adequate anticoagulation

Aplastic anemia: management

Supportive:

- blood products
- prevention and treatment of infection

Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG):

- prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes
- is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- immunosuppression using agents such as ciclosporin may also be given

Stem cell transplantation

- allogeneic transplants have a success rate of up to 80%

Autoimmune hemolytic anemia

Autoimmune haemolytic anaemia (AIHA) may be divided into 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis. It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs. AIHA is characterised by a positive direct antiglobulin test (Coombs' test)

Warm AIHA

In warm AIHA the antibody (usually IgG) causes haemolysis best at body temperature and haemolysis tends to occur in extravascular sites, for example the spleen. Management options include steroids, immunosuppression and splenectomy

Causes of warm AIHA

- autoimmune disease: e.g. systemic lupus erythematosus*
- neoplasia: e.g. lymphoma, CLL
- drugs: e.g. methyl dopa.

Cold AIHA

The antibody in cold AIHA is usually IgM and causes haemolysis best at 4 deg C. Haemolysis is mediated by complement and is more commonly intravascular. Features may include symptoms of Raynaud's and acrocynosis. Patients respond less well to steroids

Causes of cold AIHA

- neoplasia: e.g. lymphoma
- infections: e.g. mycoplasma, EBV

*systemic lupus erythematosus can rarely be associated with a mixed-type autoimmune haemolytic anaemia

Beta-thalassemia trait

The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains. Beta-thalassemia trait is an autosomal recessive condition characterised by a mild hypochromic, microcytic anaemia. It is usually asymptomatic

Features

- mild hypochromic, microcytic anaemia - microcytosis is characteristically disproportionate to the anaemia
- HbA2 raised (> 3.5%)

External Links

Patient.co.uk

Thalassemia review

Bladder cancer: risk factors

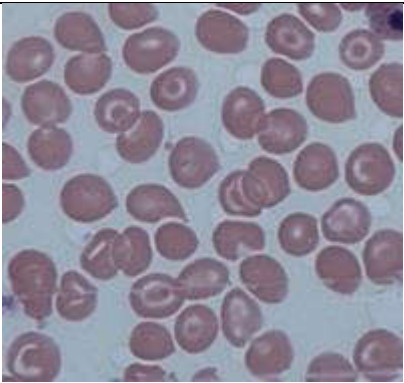
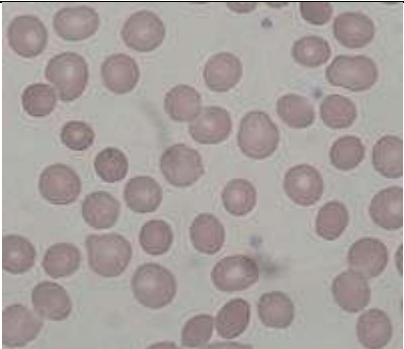
Risk factors for transitional cell carcinoma of the bladder include:

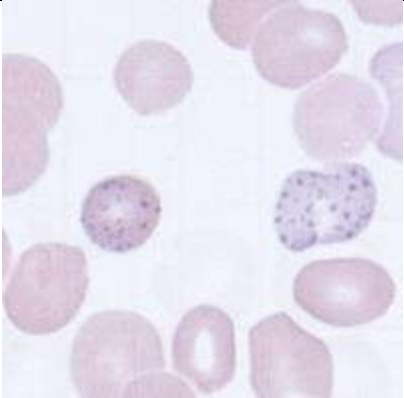
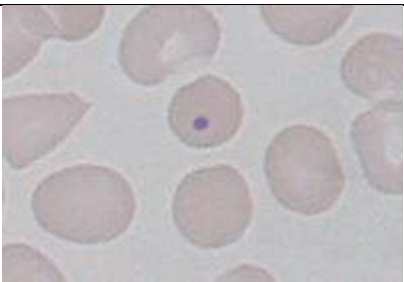
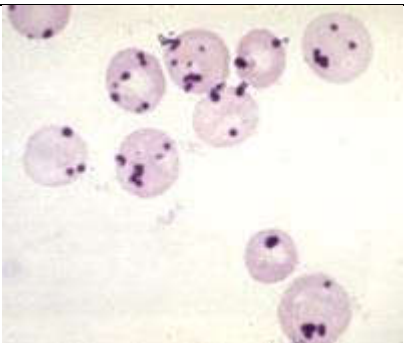
- Smoking
- Exposure to aniline dyes in the printing and textile industry
- Rubber manufacture
- Cyclophosphamide

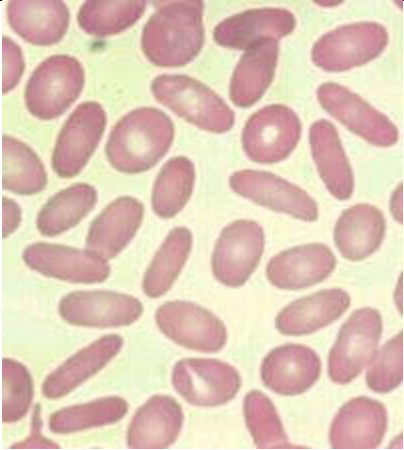
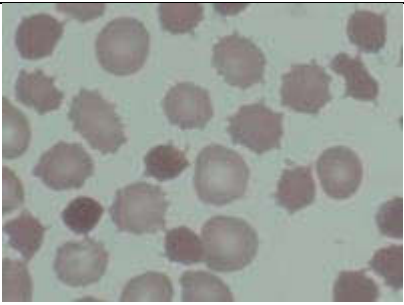
Risk factors for squamous cell carcinoma of the bladder include:

- Schistosomiasis
 - Calmette-Guérin (BCG) treatment
 - Smoking
-

Blood films: pathological cell forms
Pathological red cell forms

Abnormality	Associated condition(s)	Appearance
Target cells	Sickle-cell/thalassaemia Iron-deficiency anaemia Hyposplenism Liver disease	 
'Tear-drop' poikilocytes	Myelofibrosis	 
Spherocytes	Hereditary spherocytosis Autoimmune hemolytic anaemia	

Basophilic stippling	Lead poisoning Thalassemia Sideroblastic anemia Myelodysplasia	 
Howell-Jolly bodies	Hyposplenism	 
Heinz bodies	G6PD deficiency Alpha-thalassemia	 
Schistocytes ('helmet cells')	Intravascular haemolysis Mechanical heart valve Disseminated intravascular coagulation	

'Pencil' poikilocytes	Iron deficiency anaemia	
Burr cells (echinocytes)	Uraemia Pyruvate kinase deficiency	 
Acanthocytes	Abetalipoproteinemia	 

Other blood film abnormalities:

- hypersegmented neutrophils: megaloblastic anaemia

Blood films: typical pictures

Hyposplenism e.g. post-splenectomy:

- target cells
- Howell-Jolly bodies
- Pappenheimer bodies
- siderotic granules
- acanthocytes

Iron-deficiency anaemia:

- target cells
- 'pencil' poikilocytes
- if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

Myelofibrosis:

- 'tear-drop' poikilocytes

Intravascular hemolysis:

- schistocytes

Megaloblastic anemia:

- hypersegmented neutrophils
-

Blood product transfusion complications

Complications:

- haemolytic: immediate or delayed
- febrile reactions
- transmission of viruses, bacteria, parasites, vCJD
- hyperkalaemia
- iron overload
- ARDS
- clotting abnormalities

Immediate haemolytic reaction

- e.g. ABO mismatch
- massive intravascular haemolysis

Febrile reactions

- due to white blood cell HLA antibodies
- often the result of sensitization by previous pregnancies or transfusions

Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

Transmission of vCJD

- although the absolute risk is very small, vCJD may be transmitted via blood transfusion
- a number of steps have been taken to minimise this risk, including:
 - from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present
 - from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
 - from 2004 onward, recipients of blood components have been excluded from donating blood.

External Link

[Gov.uk](http://gov.uk)

2013 vCJD and Transfusion of Blood Components: an Updated Risk Assessment

Burkitt's lymphoma

♦ Burkitt's lymphoma is a high-grade B-cell neoplasm. **There are two major forms:**

- endemic (African) form: typically involves maxilla or mandible
- sporadic form: abdominal (e.g. ileo-caecal) tumours are the most common form. More common in patients with HIV

♦ Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14). The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

Microscopy findings:

- 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

Management is with chemotherapy. This tends to produce a rapid response which may cause 'tumour lysis syndrome'. Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin*) is often given before the chemotherapy to reduce the risk of this occurring. Complications of tumour lysis syndrome include:

- hyperkalaemia
- hyperphosphataemia
- hypocalcaemia
- hyperuricaemia
- acute renal failure

*allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective

Cancer in the UK

The most common causes of cancer in the UK are as follows*

- 1. Breast
- 2. Lung
- 3. Colorectal
- 4. Prostate
- 5. Bladder
- 6. Non-Hodgkin's lymphoma
- 7. Melanoma
- 8. Stomach
- 9. Oesophagus
- 10. Pancreas

The most common causes of death from cancer in the UK are as follows:

- 1. Lung
- 2. Colorectal
- 3. Breast
- 4. Prostate
- 5. Pancreas
- 6. Oesophagus
- 7. Stomach
- 8. Bladder
- 9. Non-Hodgkin's lymphoma
- 10. Ovarian

*excludes non-melanoma skin cancer

External Link

[Cancer Research UK](#)

Common cancers - UK mortality statistics

Chemotherapy side-effects: nausea and vomiting

Nausea and vomiting are common side-effects of chemotherapy. **Risk factors for the development of symptoms include:**

- anxiety
- age less than 50 years old
- concurrent use of opioids
- the type of chemotherapy used

For patients at low-risk of symptoms then drugs such as metoclopramide may be used first-line. For high-risk patients then 5HT₃ receptor antagonists such as ondansetron are often effective, especially if combined with dexamethasone

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are almost always B-cells (99%)

Features

- often none
- constitutional: anorexia, weight loss
- bleeding, infections
- lymphadenopathy more marked than CML

Complications

- hypogammaglobulinaemia leading to recurrent infections
- warm autoimmune haemolytic anaemia in 10-15% of patients
- transformation to high-grade lymphoma (Richter's transformation)

Investigations

- blood film: smudge cells (also known as smear cells)
- immunophenotyping

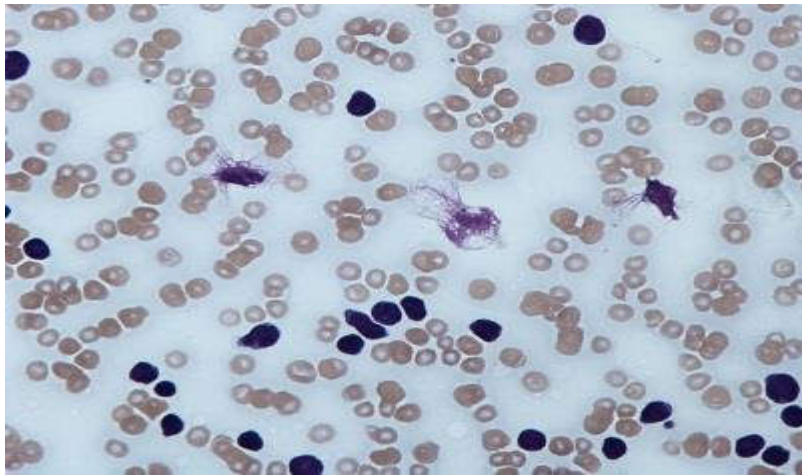


Image sourced from [Wikipedia](#)



Peripheral blood film showing smudge B cells

External Link

[British Committee for Standards in Haematology](#)

2005 CLL guidelines

Chronic lymphocytic leukaemia: management

Indications for treatment:

- progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- massive (>10 cm) or progressive lymphadenopathy
- massive (>6 cm) or progressive splenomegaly
- progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
- systemic symptoms: weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopenias e.g. ITP

Management:

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients.

External Link

[British Committee for Standards in Haematology](#)

2012 CLL guidelines

Chronic lymphocytic leukaemia: prognostic factors

Poor prognostic factors (median survival 3-5 years)

- male sex
- age > 70 years
- lymphocyte count > 50
- prolymphocytes comprising more than 10% of blood lymphocytes
- lymphocyte doubling time < 12 months
- raised LDH
- CD38 expression positive

Chromosomal changes

- deletion of the long arm of chromosome 13 (del 13q) is the most common abnormality, being seen in around 50% of patients. It is associated with a good prognosis
- deletions of part of the short arm of chromosome 17 (del 17p) are seen in around 5-10% of patients and are associated with a poor prognosis

External Link

[British Committee for Standards in Haematology](#)

2005 CLL guidelines

Chronic myeloid leukaemia

The Philadelphia chromosome is present in more than 95% of patients with chronic myeloid leukaemia (CML). It is due to a translocation between the long arm of chromosome 9 and 22 - t(9:22)(q34; q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal

Presentation (40-50 years):

- middle-age
- anaemia, weight loss, abdo discomfort
- splenomegaly may be marked
- spectrum of myeloid cells seen in peripheral blood
- decreased leukocyte alkaline phosphatase
- may undergo blast transformation (AML in 80%, ALL in 20%)

Management

- imatinib is now considered first-line treatment
- hydroxyurea
- interferon-alpha
- allogenic bone marrow transplant

Imatinib

- inhibitor of the tyrosine kinase associated with the BCR-ABL defect
 - very high response rate in chronic phase CML
-

Coagulopathy of liver disease

In liver failure all clotting factors are low, except for factor VIII which is paradoxically supra-normal. This is because factor VIII is synthesised in endothelial cells throughout the body, unlike the other clotting factors which are synthesised purely in hepatic endothelial cells. Furthermore, whilst activated factor VIII is usually rapidly cleared from the blood stream, good hepatic function is required for this to occur, further leading to increases in circulating factor VIII. This is one of many reasons why, despite conventional coagulation studies (increased PT, APTT, decreased fibrinogen) suggesting increased bleeding risk, patients with chronic liver disease are not protected from venous thrombosis formation but are paradoxically at an increased risk of thrombosis, in addition to bleeding. Other events occurring in chronic liver disease which predispose patients to thrombosis formation include reduced synthesis of the purely hepatic derived natural anticoagulants protein c and protein s (vitamin k dependent), and anti-thrombin (non-vitamin k dependent).

Reference

Tripodi et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. *Gastroenterology*. 2009 Dec;137(6):2105-11.

Colorectal cancer

Colorectal cancer is the third most common type of cancer in the UK and the second most cause of cancer deaths

Location of cancer (averages):

- rectal: 40%
 - sigmoid: 30%
 - descending colon: 5%
 - transverse colon: 10%
 - ascending colon and caecum: 15%
-

Colorectal cancer: screening

Overview

- most cancers develop from adenomatous polyps. Screening for colorectal cancer has been shown to reduce mortality by 16%
- the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years in England, 50 to 74 years in Scotland.
IPatients aged over 74 years may request screening
- eligible patients are sent faecal occult blood (FOB) tests through the post
- patients with abnormal results are offered a colonoscopy

At colonoscopy, approximately:

- 5 out of 10 patients will have a normal exam
- 4 out of 10 patients will be found to have polyps which may be removed due to their premalignant potential
- 1 out of 10 patients will be found to have cancer

External Link

[Postgraduate Medical Journal](#)

Management of colorectal cancer

[SIGN](#)

Management of colorectal cancer guidelines

[NHS](#)

Bowel Cancer Screening Programme

[Royal College of Physicians](#)

2012 Colonic polyps and an update on the bowel cancer screening programme

Cyclophosphamide

Cyclophosphamide is an alkylating agent used in the management of cancer and autoimmune conditions. It works by causing cross-linking of DNA

Adverse effects

- haemorrhagic cystitis: incidence reduced by the use of hydration and mesna
- myelosuppression
- transitional cell carcinoma

Mesna

- 2-mercaptoethane sulfonate Na
- a metabolite of cyclophosphamide called acrolein is toxic to urothelium
- mesna binds to and inactivates acrolein helping to prevent haemorrhagic cystitis

Cytotoxic agents

The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents.

Alkylating agents

Cytotoxic	Mechanism of action	Adverse effects
Cyclophosphamide	Alkylating agent - causes cross-linking in DNA	Haemorrhagic cystitis, myelosuppression, transitional cell carcinoma

Cytotoxic antibiotics

Cytotoxic	Mechanism of action	Adverse effects
Bleomycin	Degrades preformed DNA	Lung fibrosis
Doxorubicin	Stabilizes DNA-topoisomerase II complex inhibits DNA & RNA synthesis	Cardiomyopathy

Antimetabolites

Cytotoxic	Mechanism of action	Adverse effects
Methotrexate	Inhibits dihydrofolate reductase and thymidylate synthesis	Myelosuppression, mucositis, liver fibrosis, lung fibrosis
Fluorouracil (5-FU)	Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)	Myelosuppression, mucositis, dermatitis
6-mercaptopurine	Purine analogue that is activated by HGPRTase, decreasing purine synthesis	Myelosuppression
Cytarabine	Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase	Myelosuppression, ataxia

Acts on microtubules

Cytotoxic	Mechanism of action	Adverse effects
Vincristine, vinblastine	Inhibits formation of microtubules	Vincristine: Peripheral neuropathy (reversible), paralytic ileus Vinblastine: myelosuppression
Docetaxel	Prevents microtubule depolymerisation & disassembly, decreasing free tubulin	Neutropaenia

Other cytotoxic drugs

Cytotoxic	Mechanism of action	Adverse effects
Cisplatin	Causes cross-linking in DNA	Ototoxicity, peripheral neuropathy, hypomagnesaemia
Hydroxyurea (hydroxycarbamide)	Inhibits ribonucleotide reductase, decreasing DNA synthesis	Myelosuppression

Deep vein thrombosis: diagnosis and management

Diagnosis

NICE published guidelines in 2012 relating to the investigation and management of deep vein thrombosis (DVT).

If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2

Clinical probability simplified score:

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

If a DVT is 'likely' (2 points or more)

- a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours).

If a DVT is 'unlikely' (1 point or less)

- perform a D-dimer test and if it is positive arrange:
- a proximal leg vein ultrasound scan within 4 hours
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours).

Management

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed.

- a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis
- the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range
- warfarin should be continued for at least 3 months. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE add 'consider extending warfarin beyond 3 months for patients with *unprovoked* proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE
- for patients with active cancer NICE recommend using LMWH for 6 months

Further investigations and thrombophilia screening

As both malignancy and thrombophilia are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots.

Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:

- a physical examination (guided by the patient's full history) and
- a chest X-ray and
- blood tests (full blood count, serum calcium and liver function tests) and urinalysis.

Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE

Thrombophilia screening:

- not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- consider testing for antiphospholipid antibodies if unprovoked DVT or PE
- consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE.

External Link

[NICE](#)

2012 Venous thromboembolism guidelines

Drug-induced hemolytic anemia

Drug-induced haemolytic anaemia can be classified according to three different mechanisms:

Type I - antibody against drug-red cell membrane complex:

- penicillin

Type II - deposition of complement via a drug-protein-antibody complex onto the red cell membrane:

- quinidine
- rifampicin

Type III - true autoimmune haemolytic anaemia - role of drug not known:

- methyldopa
 - L-dopa
 - mefanamic acid
-

Drug-induced pancytopenia

Drug causes of pancytopenia

- cytotoxics
- antibiotics: trimethoprim, chloramphenicol
- anti-rheumatoid: gold, penicillamine
- carbimazole*
- anti-epileptics: carbamazepine
- sulphonylureas: tolbutamide

*causes both agranulocytosis and pancytopenia

ECOG score

The ECOG score is a 'performance status' scale, or a score that measures the functional status a patient. It is used to decide if a patient is a good or poor candidate for future oncological therapies.

Those with a poor functional status is a poor candidate for further chemotherapy.

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Eosinophilia

Causes of eosinophilia may be divided into pulmonary, infective and other

Pulmonary causes

- asthma
- allergic bronchopulmonary aspergillosis
- Churg-Strauss syndrome
- Löffler's syndrome
- tropical pulmonary eosinophilia
- eosinophilic pneumonia
- hypereosinophilic syndrome

Infective causes

- schistosomiasis
- nematodes: Toxocara, Ascaris, Strongyloides
- cestodes: Echinococcus

Other causes

- drugs: sulfasalazine, nitrofurantoin
 - psoriasis/eczema
 - eosinophilic leukaemia (very rare)
-

Factor V Leiden

Factor V Leiden (activated protein C resistance) is the most common inherited thrombophilia, being present in around 5% of the UK population. It is due to a mutation in the Factor V Leiden mutation. Heterozygotes have a 4-5 fold risk of venous thrombosis.

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

Condition	Prevalence	Relative risk of VTE
Factor V Leiden (heterozygous)	5%	4
Prothrombin gene mutation (heterozygous)	1.5%	3
Protein C deficiency	0.3%	10
Protein S deficiency	0.1%	5-10
Antithrombin III deficiency	0.02	10-20

G6PD deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest red blood cell enzyme defect. It is more common in people from the Mediterranean and Africa and is inherited in a X-linked recessive fashion. Many drugs can precipitate a crisis as well as infections and broad (fava) beans

Pathophysiology

- ↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress

Features

- neonatal jaundice is often seen
- intravascular haemolysis
- gallstones are common
- splenomegaly may be present
- Heinz bodies on blood films

♦Diagnosis is made by using a G6PD enzyme assay

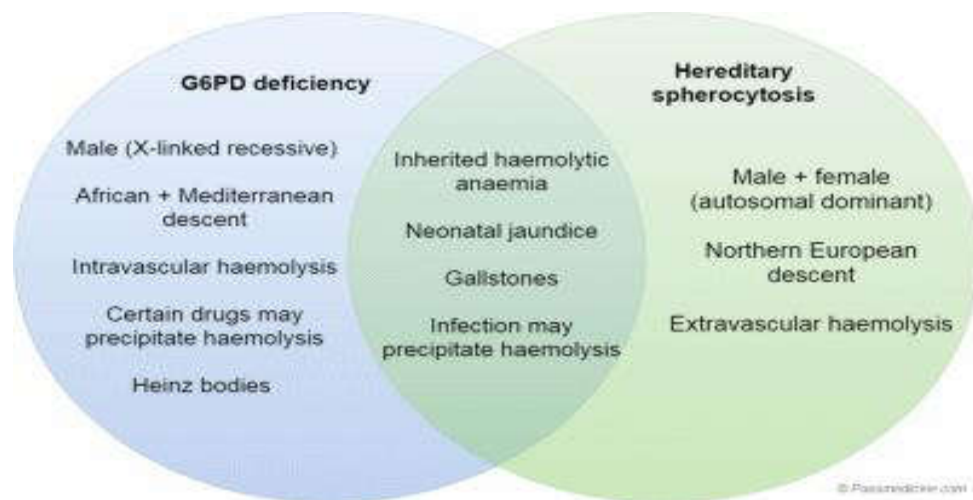
♦ **Some drugs causing haemolysis**

- anti-malarials: primaquine
- ciprofloxacin
- sulph- group drugs: sulphonamides, sulphasalazine, sulfonylureas

♦ **Some drugs thought to be safe:**

- penicillins
- cephalosporins
- macrolides
- tetracyclines
- trimethoprim

Comparing G6PD deficiency to hereditary spherocytosis:



Comparison of G6PD deficiency to hereditary spherocytosis

	G6PD deficiency	Hereditary spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	• Neonatal jaundice • Infection/drugs precipitate haemolysis • Gallstones	• Neonatal jaundice • Chronic symptoms although haemolytic crises may be precipitated by infection • Gallstones • Splenomegaly is common
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor)
Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

Gastric cancer

Epidemiology

- overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing
- peak age = 70-80 years
- more common in Japan, China, Finland and Colombia than the West
- more common in males, 2:1

Histology

- signet ring cells may be seen in gastric cancer. They contain a large vacuole of mucin which displaces the nucleus to one side. Higher numbers of signet ring cells are associated with a worse prognosis

Associations

- *H. pylori* infection
- blood group A: gAstric cAncer
- gastric adenomatous polyps
- pernicious anaemia
- smoking
- diet: salty, spicy, nitrates
- may be negatively associated with duodenal ulcer

Investigation

- diagnosis: endoscopy with biopsy
- staging: CT or endoscopic ultrasound - endoscopic ultrasound has recently been shown to be superior to CT

External Link

[British Society of Gastroenterology](#)

BSG oesophageal and gastric cancer guidelines

Gastrointestinal secretions

Up to 7 litres of gastrointestinal secretions enter the lumen of the GI tract in a 24 hour period. The absorptive function of the small bowel is such that by the time a formed stool is created, it will contain, on average 200ml water.

The common secretions together with their approximate volumes are demonstrated below:

Origin of secretion	Volume in ml / 24 hour period	Na ⁺ mmol/L	K ⁺ mmol/L	Cl ⁻ mmol/L	HCO ₃
Salivary glands	1500	10	26	10	30
Stomach	1500	60	10	130	
Duodenum	100-2000	140	80	80	
Pancreas	1000	140	5	70	115
Bile	50-800	145	50	100	35
Jejunum/ileum	3000	140	50	104	30
Colon	100	60	30	40	

♦The regulation of these secretions is dependent upon location. In the salivary glands a complex interaction of flow rate governed by the autonomic nervous system.

♦The exact composition of sodium and potassium is regulated by aldosterone. In the stomach hormones such as gastrin play a role and feedback is both endocrine and neurologically mediated (vagus). In the duodenum CCK is released in response to duodenal distension and this causes contraction of the gallbladder and release of bile.

♦Pancreatic secretions are affected by somatostatin. The secretions in the small bowel are affected by the osmolality of the luminal contents. This is in part due to the tightness of cellular junctions and in this regard the jejunum is more permeable than the ileum. The practical implication of this is that if an individual has an extensive intestinal resection and a high output, proximally sited stoma then administration of hypotonic rather than isotonic solutions will result in worsening of electrolyte disturbances as electrolyte rich secretions will enter the jejunum.

◆ In some individuals a colectomy or similar procedure results in formation of an end or loop ileostomy. Ileostomies typically lose between 500 and 1000ml over a 24 hour period and patients with high output ileostomies can rapidly become dehydrated. Ileostomy effluent typically contains 126mmol/L of sodium and 22mmol/L of potassium. Knowledge of this fluid composition should guide fluid prescribing in replacing losses.

Gingival hyperplasia

Drug causes of gingival hyperplasia:

- phenytoin
- ciclosporin
- calcium channel blockers (especially nifedipine)

Other causes of gingival hyperplasia include:

- acute myeloid leukaemia (myelomonocytic and monocytic types)

Hematological malignancies: genetics

Below is a brief summary of the common translocations associated with haematological malignancies

t(9;22) - Philadelphia chromosome

- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- poor prognostic indicator in ALL

t(15;17)

- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes.

t(8;14)

- seen in Burkitt's lymphoma
- MYC oncogene is translocated to an immunoglobulin gene

t(11;14)

- Mantle cell lymphoma
- deregulation of the cyclin D1 (BCL-1) gene

Hematological malignancies: infections

Viruses

- EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
- HTLV-1: Adult T-cell leukaemia/lymphoma
- HIV-1: High-grade B-cell lymphoma

Bacteria

- *Helicobacter pylori*: gastric lymphoma (MALT)

Protozoa

- malaria: Burkitt's lymphoma

Hemolytic anemias: by site

In intravascular haemolysis free haemoglobin is released which binds to haptoglobin. As haptoglobin becomes saturated haemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test). Free haemoglobin is excreted in the urine as haemoglobinuria, haemosiderinuria

Intravascular haemolysis: causes

- mismatched blood transfusion
- G6PD deficiency*
- red cell fragmentation: heart valves, TTP, DIC, HUS
- paroxysmal nocturnal haemoglobinuria
- cold autoimmune haemolytic anaemia

Extravascular haemolysis: causes

- haemoglobinopathies: sickle cell, thalassaemia
- hereditary spherocytosis
- haemolytic disease of newborn
- warm autoimmune haemolytic anaemia

*strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as an intravascular cause

Haemophilia

Haemophilia is a X-linked recessive disorder of coagulation. Up to 30% of patients have no family history of the condition. Haemophilia A is due to a deficiency of factor VIII whilst in haemophilia B (Christmas disease) there is a lack of factor IX

Features

- haemarthroses, haematomas
- prolonged bleeding after surgery or trauma

Blood tests

- prolonged APTT
- bleeding time, thrombin time, prothrombin time normal

Up to 10-15% of patients with haemophilia A develop antibodies to factor VIII treatment

Hairy cell leukaemia

Hairy cell leukaemia is a rare malignant proliferation disorder of B cells. It is more common in males (4:1)

Features:

- pancytopenia
- splenomegaly
- skin vasculitis in 1/3 patients
- 'dry tap' despite bone marrow hypercellularity
- tartrate resistant acid phosphatase (TRAP) stain positive.

Management:

- chemotherapy is first-line: cladribine, pentostatin
- immunotherapy is second-line: rituximab, interferon-alpha

Hepatocellular carcinoma

♦Hepatocellular carcinoma (HCC) is the third most common cause of cancer worldwide. Chronic hepatitis B is the most common cause of HCC worldwide with chronic hepatitis C being the most common cause in Europe.

♦The main risk factor for developing HCC is liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis. **Other risk factors include:**

- alpha-1 antitrypsin deficiency
- hereditary tyrosinosis
- glycogen storage disease
- aflatoxin
- drugs: oral contraceptive pill, anabolic steroids
- porphyria cutanea tarda
- male sex
- diabetes mellitus, metabolic syndrome.

Features:

- tends to present late
- features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- possible presentation is decompensation in a patient with chronic liver disease

Screening with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:

- patients liver cirrhosis secondary to hepatitis B & C or haemochromatosis
- men with liver cirrhosis secondary to alcohol.

Management options:

- early disease: surgical resection
- liver transplantation
- radiofrequency ablation
- transarterial chemoembolisation
- sorafenib: a multikinase inhibitor

*Wilson's disease is an exception

Hereditary spherocytosis

Basics:

- most common hereditary haemolytic anaemia in people of northern European descent
- autosomal dominant defect of red blood cell cytoskeleton
- the normal biconcave disc shape is replaced by a sphere-shaped red blood cell
- red blood cell survival reduced as destroyed by the spleen

Presentation:

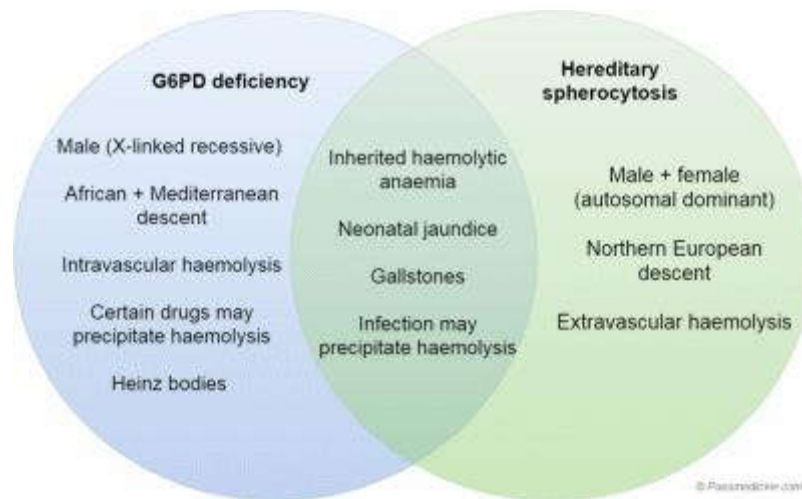
- failure to thrive
- jaundice, gallstones
- splenomegaly
- aplastic crisis precipitated by parvovirus infection
- degree of haemolysis variable
- MCHC elevated

Diagnosis

- osmotic fragility test

Management:

- folate replacement
- splenectomy



Comparison of G6PD deficiency to hereditary spherocytosis

Comparing G6PD deficiency to hereditary spherocytosis:

	G6PD deficiency	Hereditary spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	• Neonatal jaundice • Infection/drugs precipitate haemolysis • Gallstones	• Neonatal jaundice • Chronic symptoms although haemolytic crises may be precipitated by infection • Gallstones • Splenomegaly is common
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor)
Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

External Links

[British Committee for Standards in Haematology](#)

2004 Hereditary spherocytosis guidelines.

Hodgkin's lymphoma: staging

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. It has a bimodal age distributions being most common in the third and seventh decades

Ann-Arbor staging of Hodgkin's lymphoma

- I: single lymph node
- II: 2 or more lymph nodes/regions on same side of diaphragm
- III: nodes on both sides of diaphragm
- IV: spread beyond lymph nodes

Each stage may be subdivided into A or B

- A = no systemic symptoms other than pruritus
- B = weight loss > 10% in last 6 months, fever > 38c, night sweats (poor prognosis)

Hyposplenism

Causes:

- splenectomy
- sickle-cell
- coeliac disease, dermatitis herpetiformis
- Graves' disease
- systemic lupus erythematosus
- amyloid

Features

- Howell-Jolly bodies
 - siderocytes
-

IgG4-related disease

◆ IgG4-related disease has been described in virtually every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin. The histopathological features are similar across organs, regardless of the site. IgG4-related disease is analogous to sarcoidosis, in which diverse organ manifestations are linked by similar histopathological characteristics. Raised concentrations of IgG4 in tissue and serum can be helpful in diagnosing IgG4 disease, but neither is a specific diagnostic marker.

Examples include:

- Riedel's Thyroiditis
- Autoimmune pancreatitis
- Mediastinal and Retroperitoneal Fibrosis
- Periaortitis/periarteritis/Inflammatory aortic aneurysm
- Kuttner's Tumour (submandibular glands) & Mikulicz Syndrome (salivary and lacrimal glands)
- Possibly sjogren's and primary biliary cirrhosis

Iron deficiency anemia

Features

- koilonychia
- atrophic glossitis
- post-cricoid webs
- angular stomatitis

Blood film

- target cells
- 'pencil' poikilocytes
- if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

External Links

[British Society of Gastroenterology](#)

2005 IDA guidelines

ITP

◆ Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex.

◆ ITP can be divided into acute and chronic forms:

Acute ITP

- more commonly seen in children
- equal sex incidence
- may follow an infection or vaccination
- usually runs a self-limiting course over 1-2 weeks

Chronic ITP

- more common in young/middle-aged women
- tends to run a relapsing-remitting course

Evan's syndrome

- ITP in association with autoimmune haemolytic anaemia (AIHA)

External Links

[British Committee for Standards in Haematology](#)

2003 ITP guidelines

ITP: investigation and management

Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb-IIIa or Ib complex

Investigations:

- antiplatelet autoantibodies (usually IgG)
- bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukaemia

Management

- oral prednisolone (80% of patients respond)
- splenectomy if platelets < 30 after 3 months of steroid therapy
- IV immunoglobulins
- immunosuppressive drugs e.g. cyclophosphamide

External Links

[British Committee for Standards in Haematology](#)

2003 ITP guidelines

Leucocyte alkaline phosphatase

Raised in:

- myelofibrosis
- leukaemoid reactions
- polycythaemia rubra vera
- infections
- steroids, Cushing's syndrome
- pregnancy, oral contraceptive pill

Low in:

- chronic myeloid leukaemia
- pernicious anaemia
- paroxysmal nocturnal haemoglobinuria
- infectious mononucleosis

Leukaemoid reaction

The leukaemoid reaction describes the presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood. This may be due to infiltration of the bone marrow causing the immature cells to be 'pushed out' or sudden demand for new cells

Causes:

- severe infection
- severe haemolysis
- massive haemorrhage
- metastatic cancer with bone marrow infiltration

A relatively common clinical problem is differentiating chronic myeloid leukaemia from a leukaemoid reaction. The following differences may help:

Leukaemoid reaction

- high leucocyte alkaline phosphatase score
- toxic granulation (Dohle bodies) in the white cells
- 'left shift' of neutrophils i.e. three or less segments of the nucleus

Chronic myeloid leukaemia

- low leucocyte alkaline phosphatase score
-

Macrocytic anemia

Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Normoblastic causes
• vitamin B12 deficiency • folate deficiency	• alcohol • liver disease • hypothyroidism • pregnancy • reticulocytosis • myelodysplasia • drugs: cytotoxics

MGUS

◆ Monoclonal gammopathy of undetermined significance (**MGUS**, also known as benign paraproteinaemia and monoclonal gammopathy) is a common condition that causes a paraproteinaemia and is often mistaken for myeloma. Differentiating features are listed below. Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years

Features

- usually asymptomatic
- no bone pain or increased risk of infections
- around 10-30% of patients have a demyelinating neuropathy

Differentiating features from myeloma

- normal immune function
- normal beta-2 microglobulin levels
- lower level of paraproteinaemia than myeloma (e.g. < 30g/l IgG, or < 20g/l IgA)
- stable level of paraproteinaemia
- no clinical features of myeloma (e.g. lytic lesions on x-rays or renal disease)

Myelofibrosis

Overview

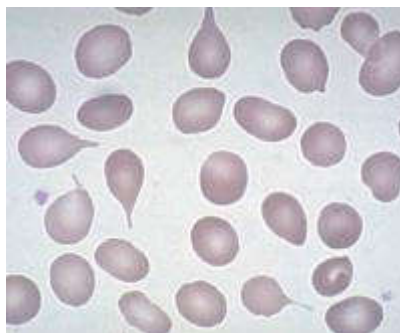
- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- hematopoiesis develops in the liver and spleen

Features

- e.g. elderly person with symptoms of anaemia e.g. fatigue (the most common presenting symptom)
- massive splenomegaly
- hypermetabolic symptoms: weight loss, night sweats etc

Laboratory findings

- anaemia
- high WBC and platelet count early in the disease
- 'tear-drop' poikilocytes on blood film
- unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
- high urate and LDH (reflect increased cell turnover).



Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis

Myeloma: features

Multiple myeloma is a neoplasm of the bone marrow plasma cells. The peak incidence is patients aged 60-70 years.

Clinical features

- bone disease: bone pain, osteoporosis + pathological fractures (typically vertebral), osteolytic lesions
- lethargy
- infection
- hypercalcaemia (see below)
- renal failure
- other features: amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity

Investigations

- monoclonal proteins (usually IgG or IgA) in the serum and urine (Bence Jones proteins)
- increased plasma cells in the bone marrow
- bone lesions on the skeletal survey

♦The diagnostic criteria for multiple myeloma requires one major and one minor criteria or three minor criteria in an individual who has signs or symptoms of multiple myeloma.

Major criteria

- Plasmacytoma (as demonstrated on evaluation of biopsy specimen)
- 30% plasma cells in a bone marrow sample
- Elevated levels of M protein in the blood or urine

Minor criteria

- 10% to 30% plasma cells in a bone marrow sample.
- Minor elevations in the level of M protein in the blood or urine.
- Osteolytic lesions (as demonstrated on imaging studies).
- Low levels of antibodies (not produced by the cancer cells) in the blood.

Hypercalcaemia in myeloma

- primary factor: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels

External Links

[NICE](#)

2016 myeloma guidelines

Myeloma: prognosis

B2-microglobulin is a useful marker of prognosis - raised levels imply poor prognosis. Low levels of albumin are also associated with a poor prognosis

International prognostic index

Stage	Criteria	Median survival (months)
I	B2 microglobulin < 3.5 mg/l Albumin > 35 g/l	62
II	Not I or III	45
III	B2 microglobulin > 5.5 mg/l	29

External Links

[British Committee for Standards in Haematology](#)

2010 myeloma guidelines.

Neutropenic sepsis

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of chemotherapy. It may be defined as a neutrophil count of $< 0.5 \times 10^9$ in a **patient who is having anticancer treatment and has one of the following:**

- a temperature higher than 38°C or
- other signs or symptoms consistent with clinically significant sepsis

Prophylaxis

- if it is anticipated that patients are likely to have a neutrophil count of $< 0.5 \times 10^9$ as a consequence of their treatment they should be offered a fluoroquinolone.

Management

- antibiotics must be started immediately, do not wait for the WBC
- NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately
- many units add vancomycin if the patient has central venous access but NICE do not support this approach
- following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment
- if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting therapy antifungal therapy blindly
- there may be a role for G-CSF in selected patients

External Links

[NICE](#)

2012 Neutropenic sepsis guideline

[Christies](#)

2013 Neutropenic sepsis guidelines

Oesophageal cancer

Until recent times oesophageal cancer was most commonly due to a squamous cell carcinoma but the incidence of adenocarcinoma is rising rapidly. Adenocarcinoma is now the most common type of oesophageal cancer and is more likely to develop in patients with a history of gastro-oesophageal reflux disease (GORD) or Barrett's.

The majority of tumours are in the middle third of the oesophagus.

Risk factors:

- smoking
- alcohol
- GORD
- Barrett's oesophagus
- achalasia
- Plummer-Vinson syndrome
- squamous cell carcinoma is also linked to diets rich in nitrosamines
- rare: coeliac disease, scleroderma

Diagnosis

- Upper GI endoscopy is the first line test
- Contrast swallow may be of benefit in classifying benign motility disorders but has no place in the assessment of tumours
- Staging is initially undertaken with CT scanning of the chest, abdomen and pelvis. If overt metastatic disease is identified using this modality then further complex imaging is unnecessary
- If CT does not show metastatic disease, then local stage may be more accurately assessed by use of endoscopic ultrasound.
- Staging laparoscopy is performed to detect occult peritoneal disease. PET CT is performed in those with negative laparoscopy. Thoracoscopy is not routinely performed.

Treatment

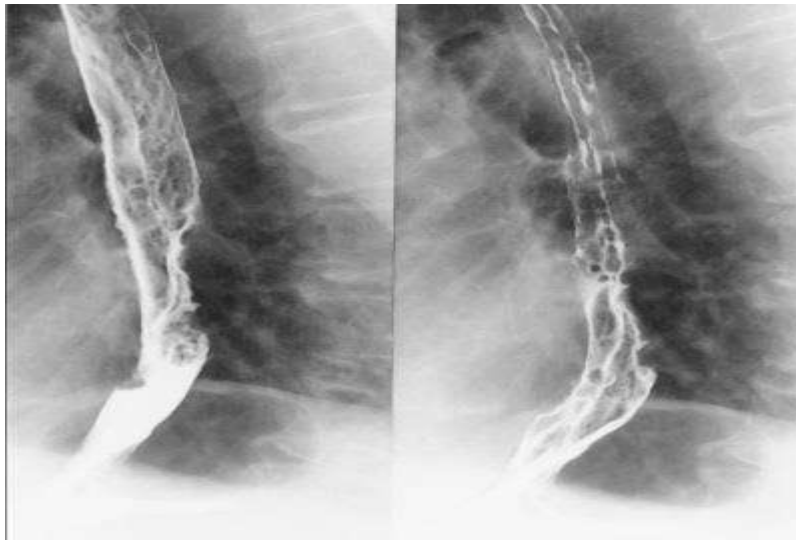
- Operable disease is best managed by surgical resection.
- The most standard procedure is an Ivor- Lewis type oesophagectomy. This procedure involves the mobilisation of the stomach and division of the oesophageal hiatus. The abdomen is closed and a right sided thoracotomy performed. The stomach is brought into the chest and the oesophagus mobilised further. An intrathoracic oesophagogastric anastomosis is constructed. Alternative surgical strategies include a transhiatal resection (for distal lesions), a left thoraco-abdominal resection (difficult access due to thoracic aorta) and a total oesophagectomy (McKeown) with a cervical oesophagogastric anastomosis.
- The biggest surgical challenge is that of anastomotic leak, with an intrathoracic anastomosis this will result in mediastinitis. With high mortality. The McKeown technique has an intrinsically lower systemic insult in the event of anastomotic leakage.
- In addition to surgical resection many patients will be treated with adjuvant chemotherapy.



© Image used on license from [Radiopaedia](#)



Barium swallow - 5cm irregular narrowing of the mid-thoracic oesophagus with proximal shouldering



© Image used on license from [Radiopaedia](https://radiopaedia.org/)



Fluoroscopy - a region of fixed, irregular stricturing is seen in the distal oesophagus

External Links

[British Society of Gastroenterology](https://www.bsg.org.uk/guidelines/oesophageal-and-gastric-cancer-guidelines)

BSG oesophageal and gastric cancer guidelines

Paraproteinaemia

Causes of paraproteinaemia

- myeloma
- monoclonal gammopathy of uncertain significance (MGUS)
- benign monoclonal gammopathy
- Waldenstrom's macroglobulinaemia
- amyloidosis
- CLL, lymphoma
- heavy chain disease
- POEMS

Benign monoclonal gammopathy

- non-lymphoid malignancy (e.g. colon, breast)
- infections (CMV, hepatitis)
- autoimmune disorders (RA, SLE)

Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. It is thought to be caused by increased sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

Pathophysiology

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

Features

- haemolytic anaemia
- red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopenia may be present
- haemoglobinuria: classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- thrombosis e.g. Budd-Chiari syndrome
- aplastic anaemia may develop in some patients

Diagnosis

- flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced haemolysis (normal red cells would not)

Management

- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- stem cell transplantation

Polycythaemia

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary

Relative causes

- dehydration
- stress: Gaisbock syndrome

Primary

- polycythaemia rubra vera

Secondary causes

- COPD
- altitude
- obstructive sleep apnoea
- excessive erythropoietin: cerebellar haemangioma, hypernephroma, hepatoma, uterine fibroids*

To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia red cell mass studies are sometimes used. In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg

*uterine fibroids may cause menorrhagia which in turn leads to blood loss - polycythaemia is rarely a clinical problem

External Links

[British Committee for Standards in Haematology](#)

2005 polycythaemia guidelines

Polycythaemia rubra vera: features

Polycythaemia rubra vera (PRV) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets. It has recently been established that a mutation in JAK2 is present in approximately 95% of patients with PRV and this has resulted in significant changes to the diagnostic criteria. The incidence of PRV peaks in the sixth decade.

Features

- hyperviscosity
- pruritus, typically after a hot bath
- splenomegaly
- haemorrhage (secondary to abnormal platelet function)
- plethoric appearance
- hypertension in a third of patients

Following history and examination, **the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed:**

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- abdominal ultrasound
- serum erythropoietin level
- bone marrow aspirate and trephine
- cytogenetic analysis
- erythroid burst-forming unit (BFU-E) culture.

Other features that may be seen in PRV include: a low ESR and a raised leukocyte alkaline phosphatase.

The diagnostic criteria for PRV have recently been updated by the BCSH. This replaces the previous PRV Study Group criteria.

JAK2-positive PRV - diagnosis requires both criteria to be present

Criteria	Notes
A1	High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Criteria	Notes
A1	Raised red cell mass (>25% above predicted) OR haematocrit >0.60 in men, >0.56 in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count $>450 \times 10^9/l$)
B2	Neutrophil leucocytosis (neutrophil count $> 10 \times 10^9/l$ in non-smokers; $> 12.5 \times 10^9/l$ in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

External Links

[British Committee for Standards in Haematology](#)

Polycythaemia rubra vera diagnosis

Polycythemia rubra vera: management

Polycythaemia rubra vera is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets.. It has peak incidence in the sixth decade, with typical features including hyperviscosity, pruritus and splenomegaly.

Management

- aspirin
- venesection - first line treatment
- hydroxyurea -slight increased risk of secondary leukaemia
- phosphorus-32 therapy

Prognosis

- thrombotic events are a significant cause of morbidity and mortality
- 5-15% of patients progress to myelofibrosis
- 5-15% of patients progress to acute leukaemia (risk increased with chemotherapy treatment)

Pregnancy: DVT/PE

Overview

- pregnancy is a hypercoagulable state
- majority occur in last trimester

Pathophysiology

- increase in factors VII, VIII, X and fibrinogen
- decrease in protein S
- uterus presses on IVC causing venous stasis in legs

Management

- warfarin contraindicated
 - S/C low-molecular weight heparin preferred to IV heparin (less bleeding and thrombocytopenia)
-

External Link

[Royal College of Obstetricians and Gynaecologists](#)

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperiu

Primary immunodeficiency

Primary immunodeficiency disorders may be classified according to which component of the immune system they affect.

Neutrophil disorders

Disorder	Underlying defect	Notes
Chronic granulomatous disease	Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species	Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. <i>Staphylococcus aureus</i> and fungi (e.g. <i>Aspergillus</i>) Negative nitroblue-tetrazolium test Abnormal dihydrorhodamine flow cytometry test
Chediak-Higashi syndrome	Microtubule polymerization defect which leads to a decrease in phagocytosis	Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen Giant granules in neutrophils and platelets
Leukocyte adhesion deficiency	Defect of LFA-1 integrin (CD18) protein on neutrophils	Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen Absence of neutrophils/pus at sites of infection

B-cell disorders

Disorder	Underlying defect	Notes
Common variable immunodeficiency	Many varying causes	Hypogammaglobulinemia is seen. May predispose to autoimmune disorders and lymphoma
Bruton's (x-linked) congenital agammaglobulinaemia	Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development	X-linked recessive. Recurrent bacterial infections are seen. Absence of B-cells with reduced immunoglobulins of all classes
Selective immunoglobulin A deficiency	Maturation defect in B cells	Most common primary antibody deficiency. Recurrent sinus and respiratory infections. Associated with coeliac disease and may cause false negative coeliac antibody screen

T-cell disorders

Disorder	Underlying defect	Notes
DiGeorge syndrome	22q11.2 deletion, failure to develop 3rd and 4th pharyngeal pouches	Common features include congenital heart disease (e.g. tetralogy of Fallot), learning difficulties, hypocalcaemia, recurrent viral/fungal diseases, cleft palate

Combined B- and T-cell disorders

Disorder	Underlying defect	Notes
Severe combined immunodeficiency	Many varying causes. Most common (X-linked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include adenosine deaminase deficiency	Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor excision circles Stem cell transplantation may be successful
Ataxia telangiectasia	Defect in DNA repair enzymes	Autosomal recessive. Features include cerebellar ataxia, telangiectasia (spider angiomas), recurrent chest infections and 10% risk of developing malignancy, lymphoma or leukaemia
Wiskott-Aldrich syndrome	Defect in WAS gene	X-linked recessive. Features include recurrent bacterial infections, eczema, thrombocytopaenia. Low IgM levels Increased risk of autoimmune disorders and malignancy

Prostate cancer: PSA testing

◆ Prostate specific antigen (PSA) is a serine protease enzyme produced by normal and malignant prostate epithelial cells. It has become an important tumour marker but much controversy still exists regarding its usefulness as a screening tool.

◆ The NHS Prostate Cancer Risk Management Programme (PCRMP) has published updated guidelines in 2009 on how to handle requests for PSA testing in asymptomatic men. A recent European trial (ERSPC) showed a statistically significant reduction in the rate of death prostate cancer by 20% in men aged 55 to 69 years but this was associated with a high risk of over-diagnosis and over-treatment. Having reviewed this and other data the National Screening Committee have decided not to introduce a prostate cancer screening programme yet but rather allow men to make an informed choice.

Age-adjusted upper limits for PSA were recommended by the PCRMP:

Age	PSA level (ng/ml)
50-59 years	3.0
60-69 years	4.0
> 70 years	5.0

PSA levels may also be raised by*:

- benign prostatic hyperplasia (BPH)
- prostatitis and urinary tract infection (NICE recommend to postpone the PSA test for at least 1 month after treatment)
- ejaculation (ideally not in the previous 48 hours)
- vigorous exercise (ideally not in the previous 48 hours)
- urinary retention
- instrumentation of the urinary tract

Poor specificity and sensitivity:

- around 33% of men with a PSA of 4-10 ng/ml will be found to have prostate cancer. With a PSA of 10-20 ng/ml this rises to 60% of men
- around 20% with prostate cancer have a normal PSA
- various methods are used to try and add greater meaning to a PSA level including age-adjusted upper limits and monitoring change in PSA level with time (PSA velocity or PSA doubling time)

*whether digital rectal examination actually causes a rise in PSA levels is a matter of debate

External Links

[NICE](#)

2014 prostate cancer guidelines

Protein C deficiency

Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis

Features:

- venous thromboembolism
- skin necrosis following the commencement of warfarin: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis

External Link

[DermnetNZ](#)

Warfarin induced skin necrosis

Pseudohyperkalaemia

Pseudohyperkalaemia is a rise in serum potassium that occurs due to excessive leakage of potassium from cells, during or after blood is taken. It is a laboratory artefact and does not represent the true serum potassium concentration. The majority of potassium is intracellular and thus leakage from cells can significantly impact serum levels. In this case the potassium is released as the large numbers of platelets aggregate and degranulate.

Causes include:

- haemolysis during venepuncture (excessive vacuum of blood drawing or too fine a needle gauge)
- delay in the processing of the blood specimen
- abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders)
- familial causes

Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium. For obtaining a lab sample, using a lithium heparin tube, requesting a slow spin (on the lab centrifuge) and walking the sample to the lab should ensure an accurate result.

Sickle-cell crises

Sickle cell anemia is characterised by periods of good health with intervening crises

Four main types of crises are recognised:

- thrombotic, 'painful crises'
- sequestration
- aplastic
- haemolytic

Thrombotic crises:

- also known as painful crises or vaso-occlusive crises
- precipitated by infection, dehydration, deoxygenation
- infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain)

Sequestration crises:

- sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
- acute chest syndrome: dyspnoea, chest pain, pulmonary infiltrates, low pO₂ - the most common cause of death after childhood

Aplastic crises:

- caused by infection with parvovirus
- sudden fall in haemoglobin

Haemolytic crises:

- rare
- fall in haemoglobin due an increased rate of haemolysis

External Links

[British Society for Haematology](#)

2015 Management of acute chest syndrome in sickle cell disease

[Clinical Knowledge Summaries](#)

Sickle Cell Disease guidelines

Sideroblastic anemia

Sideroblastic anemia is a condition where red cells fail to completely form haem, whose biosynthesis takes place partly in the mitochondrion. This leads to deposits of iron in the mitochondria that form a ring around the nucleus called a ring sideroblast. It may be congenital or acquired

Congenital cause: delta-aminolevulinate synthase-2 deficiency

Acquired causes

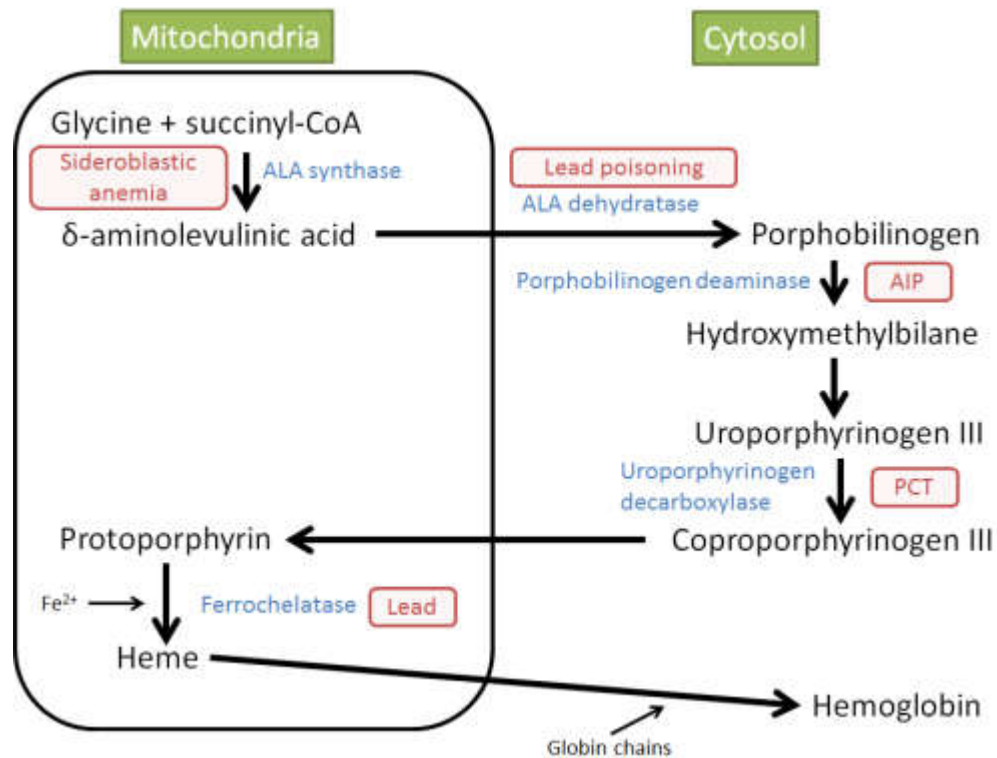
- myelodysplasia
- alcohol
- lead
- anti-TB medications

Investigations

- hypochromic microcytic anaemia (more so in congenital)
- bone marrow: sideroblasts and increased iron stores

Management

- supportive
- treat any underlying cause
- pyridoxine may help



Sjogren's syndrome

Sjogren's syndrome is an autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces. It may be primary (PSS) or secondary to rheumatoid arthritis or other connective tissue disorders, where it usually develops around 10 years after the initial onset. Sjogren's syndrome is much more common in females (ratio 9:1). There is a marked increased risk of lymphoid malignancy (40-60 fold)

Features

- dry eyes: keratoconjunctivitis sicca
- dry mouth
- vaginal dryness
- arthralgia
- Raynaud's, myalgia
- sensory polyneuropathy
- renal tubular acidosis (usually subclinical)

Investigation

- rheumatoid factor (RF) positive in nearly 100% of patients
- ANA positive in 70%
- anti-Ro (SSA) antibodies in 70% of patients with PSS
- anti-La (SSB) antibodies in 30% of patients with PSS
- Schirmer's test: filter paper near conjunctival sac to measure tear formation
- histology: focal lymphocytic infiltration
- also: hypergammaglobulinaemia, low C4

Management

- artificial saliva and tears
- pilocarpine may stimulate saliva production

Superior vena cava obstruction

Superior vena cava (SVC) obstruction is an oncological emergency caused by compression of the SVC. It is most commonly associated with lung cancer.

Features

- dyspnoea is the most common symptom
- swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- headache
- visual disturbance
- pulseless jugular venous distension

Causes

- common malignancies: small cell lung cancer, lymphoma
- other malignancies: metastatic seminoma, Kaposi's sarcoma, breast cancer
- aortic aneurysm
- mediastinal fibrosis
- goitre
- SVC thrombosis

Management

- general: dexamethasone, balloon venoplasty, stenting
 - small cell: chemotherapy + radiotherapy
 - non-small cell: radiotherapy
-

Thrombocytosis

Thrombocytosis is an abnormally high platelet count, usually $> 400 \times 10^9/l$.

Causes of thrombocytosis:

- reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery
- malignancy
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
- hyposplenism

Essential thrombocytosis

Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis. Megakaryocyte proliferation results in an overproduction of platelets.

Features

- platelet count $> 600 \times 10^9/l$
- both thrombosis (venous or arterial) and haemorrhage can be seen
- a characteristic symptom is a burning sensation in the hands
- a JAK2 mutation is found in around 50% of patients

Management

- hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count
 - interferon- α is also used in younger patients
 - low-dose aspirin may be used to reduce the thrombotic risk
-

Thrombophilia: causes

Inherited

Gain of function polymorphisms:

- factor V Leiden (activated protein C resistance): most common cause of thrombophilia
- prothrombin gene mutation: second most common cause

Deficiencies of naturally occurring anticoagulants:

- antithrombin III deficiency
- protein C deficiency
- protein S deficiency

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

Condition	Prevalence	Relative risk of VTE
Factor V Leiden (heterozygous)	5%	4
Prothrombin gene mutation (heterozygous)	1.5%	3
Protein C deficiency	0.3%	10
Protein S deficiency	0.1%	5-10
Antithrombin III deficiency	0.02	10-20

Acquired

Antiphospholipid syndrome

Drugs:

- the combined oral contraceptive pill
-

Thrombotic thrombocytopenic purpura: management

Pathogenesis of thrombotic thrombocytopenic purpura (TTP):

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

External Links

[British Society for Haematology](#)

2015 Management of acute chest syndrome in sickle cell disease

[Clinical Knowledge Summaries](#)

Sickle Cell Disease guideline

[British Committee for Standards in Haematology](#)

2012 TTP guidelines

Thymoma

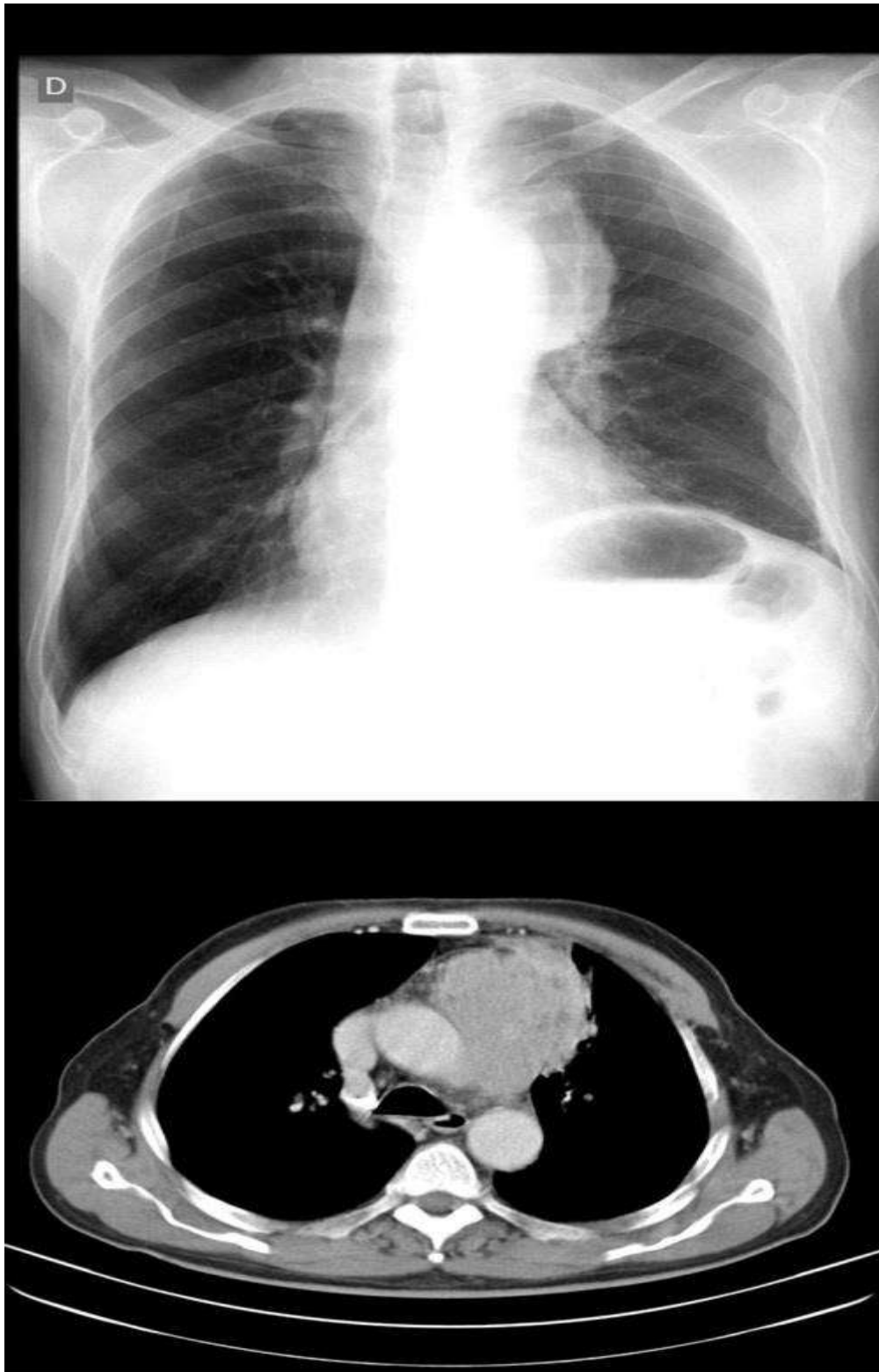
Thymomas are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

Associated with:

- myasthenia gravis (30-40% of patients with thymoma)
- red cell aplasia
- dermatomyositis
- also : SLE, SIADH

Causes of death

- compression of airway
- cardiac tamponade



© Image used on license from [Radiopaedia](#)

Chest x-ray and accompanying CT scan of a patient with a thymoma. In the chest x-ray there is a partially delineated mediastinal mass (anterior mediastinum) with regular borders, bulging the left upper mediastinal contour.



© Image used on license from [Radiopaedia](#)



CT slice at the bifurcation of the main bronchus showing an invasive thymoma presenting as an anterior mediastinal mass

External Links

[Radiopaedia](#)

Thymic tumours

Tumour lysis syndrome

♦Tumour lysis syndrome (TLS) is a potentially deadly condition related to the treatment of high grade lymphomas and leukaemias. It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy. On occasion it can occur with steroid treatment alone. Awareness of the condition is critical as prophylactic medication can be given to prevent the potentially deadly effects of tumour cell lysis.

♦Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy. Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys. Patients in lower risk groups should be given oral allopurinol during chemotherapy cycles in an attempt to avoid the condition.

♦TLS occurs from the breakdown of the tumour cells and the subsequent release of chemicals from the cell. It leads to a high potassium and high phosphate level in the presence of a low calcium. It should be suspected in any patient presenting with an acute kidney injury in the presence of a high phosphate and high uric acid level.

From 2004 TLS has been graded using the Cairo-Bishop scoring system -

Laboratory tumor lysis syndrome: abnormality in two or more of the following, occurring within three days before or seven days after chemotherapy.

- uric acid > 475umol/l or 25% increase
- potassium > 6 mmol/l or 25% increase
- phosphate > 1.125mmol/l or 25% increase
- calcium < 1.75mmol/l or 25% decrease

Clinical tumor lysis syndrome: laboratory tumor lysis syndrome plus one or more of the following:

- increased serum creatinine (1.5 times upper limit of normal)
 - cardiac arrhythmia or sudden death
 - seizure
-

Tumour markers

Tumour markers may be divided into:

- monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- tumour antigens
- enzymes (alkaline phosphatase, neurone specific enolase)
- hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity

Monoclonal antibodies

Tumour marker	Association
CA 125	Ovarian cancer
CA 19-9	Pancreatic cancer
CA 15-3	Breast cancer

Tumour antigens

Tumour marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
Alpha-feto protein (AFP)	Hepatocellular carcinoma, teratoma
Carcinoembryonic antigen (CEA)	Colorectal cancer
S-100	Melanoma, schwannomas
Bombesin	Small cell lung carcinoma, gastric cancer, neuroblastoma

External Links

[National Cancer Institute](#)

Tumour markers

Venous thromboembolism: risk factors

Common predisposing factors include malignancy, pregnancy and the period following an operation. The comprehensive list below is partly based on the 2010 SIGN venous thromboembolism (VTE) guidelines:

General:

- increased risk with advancing age
- obesity
- family history of VTE
- pregnancy (especially puerperium)
- immobility
- hospitalisation
- anaesthesia
- central venous catheter: femoral >> subclavian

Underlying conditions:

- malignancy
- thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- heart failure
- antiphospholipid syndrome
- Behcet's
- polycythaemia
- nephrotic syndrome
- sickle cell disease
- paroxysmal nocturnal haemoglobinuria
- hyperviscosity syndrome
- homocystinuria

Medication:

- combined oral contraceptive pill: 3rd generation more than 2nd generation
- hormone replacement therapy: the risk of VTE is higher in women taking oestrogen + progestogen preparations compared to those taking oestrogen only preparations
- raloxifene and tamoxifen
- antipsychotics (especially olanzapine) have recently been shown to be a risk factor

It should be remembered however that around 40% of patients diagnosed with a PE have no major risk factors.

External Links

[SIGN](#)

2010 Prevention and management of venous thromboembolism guidelines

Vitamin B12 deficiency

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system. It is absorbed after binding to intrinsic factor (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum. A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor.

Causes of vitamin B12 deficiency:

- pernicious anaemia
- post gastrectomy
- poor diet
- disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc
- metformin (rare)

Features of vitamin B12 deficiency:

- macrocytic anaemia
- sore tongue and mouth
- neurological symptoms: e.g. Ataxia
- neuropsychiatric symptoms: e.g. Mood disturbances

Management:

- if no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months
- if a patient is also deficient in folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord

Von Willebrand's disease

Von Willebrand's disease is the most common inherited bleeding disorder. The majority of cases are inherited in an autosomal dominant fashion* and characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemarthroses and muscle haematomas are rare

Role of von Willebrand factor

- large glycoprotein which forms massive multimers up to 1,000,000 Da in size
- promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII

Types

- type 1: partial reduction in vWF (80% of patients)
- type 2: abnormal form of vWF
- type 3: total lack of vWF (autosomal recessive)

Investigation

- prolonged bleeding time
- APTT may be prolonged
- factor VIII levels may be moderately reduced
- defective platelet aggregation with ristocetin

Management:

- tranexamic acid for mild bleeding
- desmopressin (DDAVP): raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells
- factor VIII concentrate

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

External Links

[British Committee for Standards in Haematology](#)

2014 Von Willebrand's disease guidelines

Waldenstrom's macroglobulinaemia

Waldenstrom's macroglobulinaemia is an uncommon condition seen in older men. It is a lymphoplasmacytoid malignancy characterized by the secretion of a monoclonal IgM paraprotein

Features

- monoclonal IgM paraproteinaemia
 - systemic upset: weight loss, lethargy
 - hyperviscosity syndrome e.g. visual disturbance
 - hepatosplenomegaly
 - lymphadenopathy
 - cryoglobulinaemia e.g. Raynaud's
-